AstraZeneca

January 24, 2002

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Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 01D-0488
Response to FDA Call for Comments
Draft Guidance for Industry on Food-Effect, Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling

Dear Sir or Madam:

Reference is made to the November 28, 2001 Federal Register notice (FR Doc. 01D-0488) announcing the availability of the Food and Drug Administration Draft Guidance entitled, "Draft Guidance for Industry on Food-Effect, Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling".

AstraZeneca LP has reviewed the draft guidance and our comments are outlined in the attached document.

We hope that you find this information useful in clarifying and adding to the pending final guidance document. Thank you for your consideration.

Please direct any questions or requests for additional information to me, or in my absence to Bob Orzolek, Director, U.S. Regulatory Affairs-Labeling, at 302/886-4550.

Sincerely,

Carolyn Russello-Callahan, MS
Associate Director
U.S. Regulatory Affairs - Labeling

01D-0488

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Comments from AstraZeneca on the FDA Draft Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling

Section	Line Number	Comment or proposed replacement text
Introduction	Line 46	Only the average bioequivalence approach is recommended for assessing the food effect. Can a sponsor apply the population BE (PBE) or the individual BE (IBE) approach to food effect studies since these approaches are also suggested by the current FDA BE guidance?
Introduction	Line 47	The 80-125% rule may be too stringent for food effect studies. In particular, it may be very challenging to meet the criteria for C_{max}. What is the rationale for selecting this?
Recommendations for Food-Effect BA and Fed BE Studies, Immediate-Release Drug Products, INDs/NDAs	Lines 113-115	Read: "This guidance recommends that food-effect BA and fed BE studies be conducted early in the drug development process using the formulation to be employed in the clinical trials intended to provide primary evidence of efficacy and safety". Suggestion: Delete "fed BE". We agree that it may be important to assess the effect of food on bioavailability before the pivotal Phase III studies are conducted. However, we do not see the rationale for bioequivalence during fed conditions between early formulations. According to lines 123-124 (page 4) it is generally not needed to establish bioequivalence between the Phase III formulation and the to-be-marketed formulation during fed conditions.
Recommendations for Food-Effect BA and Fed BE Studies, Immediate-Release Drug Products, ANDAs	Lines 141-142	The draft guidance states that a BE study under fed conditions is not recommended "When the label of the RLD does not make any statements about the effect of food on absorption or administration." Since food effects may well be formulation specific, the bioavailability of the new product may be different, compared to the RLD, during fed conditions. It may also be different from fasting conditions, even if BE between the two formulations was assessed fasting. In most cases there are no restrictions with regard to drug administration in relation to meals in the clinical trials providing evidence of efficacy and safety for the original product and patients often take their medication in connection to meals. We therefore consider it a potential danger for the patient when switching to a new product, if that product has not been studied during fed conditions.
Study Considerations, General Design	Line 176	In many instances it has been the practice to perform multiple dose food-interaction studies on modified release formulations. This guidance provides no comment on the use of multiple-dose study designs. We recommend that the Agency address this in the guidance by providing a rationale as to why multiple-dose studies are discouraged or, language indicating on what circumstances such a design would be allowable.

Study Considerations, Subject Selection	Lines 190-197	We believe the guidance should mention first the criteria, or at least cross-reference to the later section where the criterion are set out, before discussing sizing to claim an absence of food effects.
Study Considerations, Subject Selection	Line 196-197	In general, we do not believe that 12 subjects can provide sufficient power to meet the equivalence criteria. The number of subjects should be based on that needed to achieve adequate power for proper statistical assessment. We recommend deletion of the sentence "Typically, a minimum of 12 subjects should complete the food-effect BA and fed BE studies."
Study Considerations, Dosage Strength	Line 201	We recommend amending the first sentence in Section IV, C Dosage Strength to the following in order to avoid confusion: "In general, the highest strength of a drug product (not necessarily the highest dose) should be tested in all food-effect BA and fed BE studies.
Study Considerations, Test Meal	Lines 209-225	Food can influence the absorption and PK as presented in the guideline. However, food components not included in the standard test meals may influence both absorption and PK in other ways. For example, components in grapefruit juice and broccoli may alter the active secretion and/or gut wall metabolism. This should be included in the guideline or in an accompanying guideline. If such interactions take time to develop, repeated dosing studies may be required.
Study Considerations, Test Meal	Lines 209-225	It is recognized that the guidance allows for other test meals, but a concern is that the labeling will be based on a high fat meal that is not indicative of the average American breakfast.
Study Considerations, Test Meal	Lines 213–217	We recommend the usage of SI-units (kJ instead of calorie and mL instead of ounces)
Study Considerations, Test Meal	Lines 215-217 and Lines 236-237	It is assumed that volunteers have to finish the meal. Could an exclusion criterion be added concerning subjects' capacity of eating?
Study Considerations, Sample Collection	Line 252	We suggest revising "so that fasting and fed studies" to read "so that fasting and fed BE studies"…
Data Analysis and Labeling	Line 263	The description of exposure is inadequate. AUC is not identified although this is the parameter that will be tested for equivalence. The first term shown in parentheses is ambiguous; on the screen this appears as AUC_{0-}. and in the printed version of the PDF it is displayed as AUC_{0-4}. Please clarify what this parameter is intended to be (and if AUC_{0-4} is intended please provide the rationale - is this based upon the fact that this is close to the small intestinal transit time and similar to the time after dose intake without intake of food). Why does this parameter need to be included in addition to AUC_{0-t} and C_{max}? AUC_{0-t} needs to be defined (although it is well defined in other guidance documents).

Data Analysis and Labeling	Lines 270-271	What is the definition of the group averages (an arithmetic mean or a geometric mean)? If it is a geometric mean, what is the definition of the standard deviation? What is the definition of the coefficients of variation?
Data Analysis and Labeling	Line 286 and Line 305	The sentence ending on line 286 refers to $AUC_{0-.}$ (or AUC_{0-4} in the printed version) and AUC_{0-t}. The primary parameter, AUC (used in the labeling examples lines 297–301 and 310–313) is not included in line 286. What about AUC_{0-inf}? In line 305, do all parameters have to meet the equivalence criteria? What about a subset of parameters (see next comment also)? Please clarify the parameters to be described in this section.
Data Analysis and Labeling	Lines 294-295	Two examples of language for the package insert are provided. In the first example both C_{max} and AUC are described as having a food effect whereas in the second example neither parameter was affected by food. It would be useful to have an example of language for the package insert to be used when AUC fully meets the equivalence and C_{max} does not, but only with a minor deviation from the criteria (e.g. mean C_{max} 112% with 90% CI of 98–127%). We think that this is a common situation. It would also be useful to provide an example of language for the package insert where the concentration-response relationship is known and the expectation is that the pharmacodynamic response remains unchanged despite the finding of a significant food effect (C_{max} and AUC).

62

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359